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The *RIZ* gene was isolated based on binding to the retinoblastoma tumor suppressor protein. *RIZ* gene normally produces two protein products, RIZ1 and RIZ2, that differ in length by the presence or absence of a conserved protein motif, the PR domain, found in a subfamily of Krüppel-like zinc finger genes. RIZ2 lacks the PR domain. RIZ gene maps to human chromosome band 1p36, a region that is commonly deleted or altered in a variety of human cancers including those of breast, neurocrest, colon, and liver tissues. RIZ1 and RIZ2 are widely expressed in normal tissues. However, RIZ1 was undetectable in 4 of 5 breast carcinoma specimens and in 4 of 10 breast cancer cell lines. Loss of RIZ1 expression was also commonly found in hepatoma tissues and cell lines. In contrast to RIZ1, RIZ2 expression appeared normal in all cases examined. These observations suggest that loss of RIZ1 may be involved in tumor formation; RIZ1 but not RIZ2 may be an inhibitor of tumor cell growth. These findings are intriguingly similar to those described for the RIZ-related PR gene MDS1-EVI1 that also produces a PR domain lacking product EVI1. EVI1 but not MDS1-EVI1 acts as an oncogene.

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Loss of RIZ1 expression in human breast cancer, Annual Report 1997, PI. Shi Huang

Introduction:

From early work on cell hybrids and on the genetics of retinoblastoma, it is now well established that loss of tumor suppressor function can lead to cancer (Knudson, 1993). There are presently more than a dozen tumor suppressor genes known, and the p53 gene and the retinoblastoma susceptibility gene (Rb) represent the two best characterized such genes (Levine, 1997; Weinberg, 1995). The RIZ1 protein is a product of the *RIZ* gene isolated in a functional screening for Rb-binding proteins (Buyse et al., 1995), and independently as a *GATA-3*-binding protein *G3B* (Shapiro et al., 1995) and as a DNA-binding protein *MTB-Zf* (Muraosa et al., 1996). *RIZ* contains an E1A like Rb-binding motif and shares an antigenic epitope with E1A. Despite this, *RIZ* gene products appear not to interact with Rb family proteins p107 and p130 (Buyse and Huang, 1997). The physiological role of the RIZ-Rb interaction is as yet undefined. RIZ1 protein has eight Kruppel-like zinc finger type DNA-binding motifs and appears to function as a DNA binding transcription factor. It is located in the nucleus (Liu et al., 1997), and can bind to GC-rich Sp-1 element and represses transcription (Xie, 1997). RIZ1 also binds to the MTE element GTCATATGAC and may activate transcription through this element (Muraosa et al., 1996).

There are several other interesting motifs in RIZ proteins, including a putative GTPase and a SH3 motif. In addition, *RIZ* encodes a PR domain of ~100 amino acids which defines a sub-family of Kruppel-like zinc finger genes; the PR domain is located at the amino-termini of these proteins. The *RIZ* gene normally produces two different products, RIZ1 and RIZ2, which differ in length by the presence or absence of the PR domain (Liu et al., 1997). An internal promoter generates RIZ2 which lacks the PR domain but is otherwise identical to RIZ1. Both products are widely expressed in adult rat tissues. Other members of the PR family include the *MDS1-EVI1* leukemia gene and the *PRDI-BF1* or *BLIMP1* transcription repressor which can drive B cell maturation (Fears et al., 1996; Huang, 1994; Keller and Maniatis, 1991; Turner et al., 1994). Remarkably similar to *RIZ, MDS1-EVI1* also gives rise to a PR lacking product, the

EVI1 oncoprotein, through an internal promoter (Bartholomew and Ihle, 1991; Fears et al., 1996).

There is circumstantial evidence that PR genes or the PR-containing products of these genes are tumor suppressors. The PR region of *MDS1-EVI1* is often disrupted by leukemia associated chromosomal insertions and translocations, resulting in the activation of the PR deficient *EVI1* gene which is considered oncogenic (Mitani et al., 1994; Morishita et al., 1992; Morishita et al., 1988; Nucifora et al., 1994). The *BLIMP1* gene maps to a tumor suppressor locus 6q21 (Mock et al., 1996), and is a transcriptional repressor of the *c-myc* oncogene (Lin et al., 1997). The *RIZ* gene maps to band 1p36 (Buyse et al., 1996; Muraosa et al., 1996), which commonly undergoes loss of heterozygosity (LOH) in a broad spectrum of human tumors, including those of breast, liver, colon, and neurocrest tissues (Bardi et al., 1993; Dracopoli et al., 1989; Fong et al., 1992; Genuardi et al., 1989; Harnett et al., 1991; Mathew et al., 1994; Simon et al., 1991). The mouse homolog of *RIZ* maps to chromosome 4 in between the marker *D4Mit48* and *Nppa* that shares linkage homology with human chromosome 1p36 (Mock et al., 1996). LOH of this region is common in mouse lung cancers (Herzog et al., 1995).

In aim 1 of our grant proposal, we asked whether RIZ gene might be altered in human breast cancer. Here, we show that loss of RIZ1 expression but not RIZ2 is common in human breast cancer and hepatoma tissues and cell lines. The data suggests that RIZ1 but not RIZ2 may be a tumor suppressor.

Results:

To study whether the *RIZ* gene might play a role in human breast cancer, we examined the expression of the two alternative forms of *RIZ*, RIZ1 and RIZ2, in tumor derived cell lines and tissues using a previously described RNase protection assay (Liu et al., 1997). A representative result of this analysis is shown in Figure 1A and 1B for human hepatoma cell lines and tissues and for breast cancer cell lines. RIZ1 and RIZ2 expression was found in normal human placenta and liver tissues (50N), and a immortalized mammary epithelial cell line 184A1N4. However, several hepatoma and breast cancer cell lines and tissues, such as HepG2, Huh2, HA22T, Hep50T, SK-BR-3,

and MB435, showed undetectable or reduced levels of RIZ1 relative to RIZ2. Loss of RIZ1 but not RIZ2 in the tumor cell lines was also confirmed by RT-PCR analysis (Figure 1C). Overall, low or absent RIZ1 was found in 8 out of 10 hepatoma cell lines, 2 of 5 lung cancer cell lines, 2 of 7 neuroblastoma cell lines, and 4 of 10 breast cancer cell lines. In contrast, RIZ2 mRNA and protein expression (not shown) was found in all tumor cell lines and tissues examined.

To further confirm loss of RIZ1 mRNA expression in tumor tissues, we performed in situ analysis of *RIZ* gene expression in breast carcinoma specimens. Fixed breast sections from 5 infiltrating carcinomas and 7 benign breast lesions (reduction mammoplasty specimens) were examined using procedures described previously (Ji et al., 1997). A PR domain anti-sense probe was used to specifically hybridize to RIZ1 mRNA. Because RIZ2 mRNA does not contain unique sequences not present in RIZ1, a fragment of coding exon 7 was used to detect both RIZ1 and RIZ2 transcripts. Positive RIZ1 hybridization was found in normal epithelial cells in 6 of 7 normal breast tissues or benign lesions. RIZ1 was not found in stromal cells. No RIZ1 expression was found in the neoplastic epithelial cells in 4 of 5 infiltrating breast carcinomas. Representative positive staining of RIZ1 in normal ductal breast epithelial cells and in normal lobular cells is shown in Figure 1D-a and 1D-b respectively. Representative negative staining of RIZ1 in two carcinoma samples is shown in Figure 1D-d and 1D-e (the pictures shown have been counter stained with hematoxylin to reveal cells which would otherwise be unrecognizable due to lack of any hybridization signals). Similar sections of the same fixed tumors (Figure 1D-f) or normal samples (Figure 1D-c) showed positive staining for the coding exon 7 probe, indicating RIZ2 expression in transformed breast epithelial cells as well as in stromal cells. We conclude from these studies that loss of RIZ1 expression may be a common change associated with human breast cancer.

We have proposed to study monoallelic expression of RIZ gene. However, analysis of available breast cancer cell lines did not reveal abnormal allelic expression of RIZ gene.

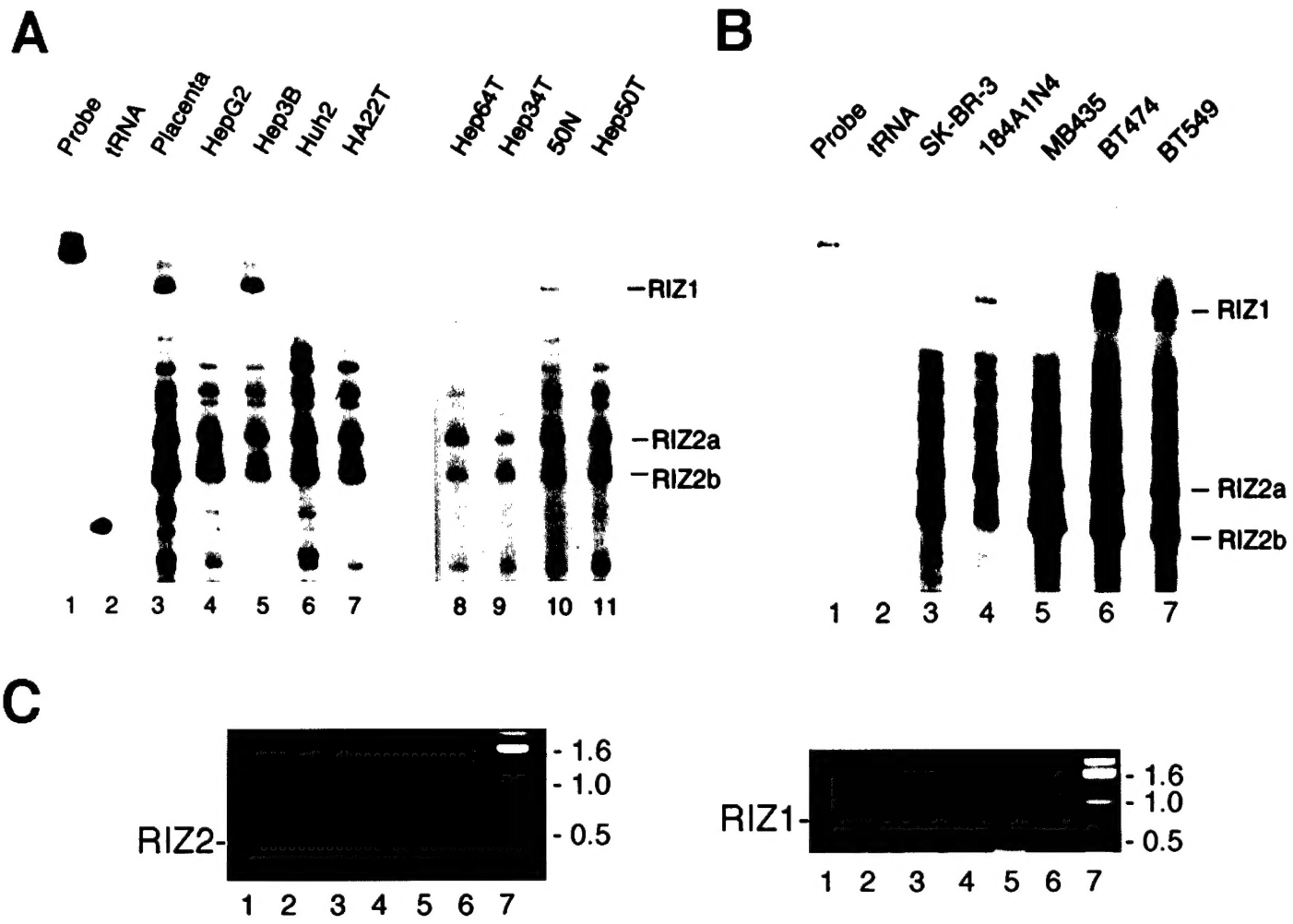

Figure 1 Huang, S.

Figure 1. RIZ1 gene expression in breast cancer and hepatoma. (A) RNase protection analysis of hepatoma cell lines and tissues. RIZ1 antisense probe was hybridized with 30 μg of total RNA prepared from different cell lines or tissues as indicated. Lanes 1-7, probe alone, tRNA, normal human placenta, hepatoma cell line HepG2, Hep3B, Huh2, and Ha22T respectively. Lanes 8-11, hepatoma tissue Hep64T, hepatoma tissue Hep34T, normal liver 50N, and hepatoma tissue Hep50T respectively. **(B)** RNase protection analysis of breast cancer cell lines. **(C)** RT-PCR analysis of RIZ1 and RIZ2 expression in human hepatoma cell lines. Lanes 1-6 represent no RNA, Hep3B, Ha22T, HepG2, Huh1, and Huh2 hepatoma cell lines respectively. DNA kb ladder (BRL) is in lane 7. **(D)** *RIZ* gene expression in human breast tissues by in situ hybridization. For tumor sections d and e, hematoxylin counterstaining was performed for viewing cells. **(a)** Positive RIZ1 staining in normal ductal breast epithelial cells but negative staining in stromal cells. **(b)** Positive RIZ1 staining in normal lobular cells. **(d)** and **(e)** Negative RIZ1 staining in highly infiltrating carcinoma cells. **(c)** and **(f)** Positive staining for coding exon 7 in normal ductal breast epithelial cells **(c)** and in highly infiltrating carcinoma cells **(f)** as well as in stromal cells **(c and f).**

Methods:

Human breast cancer and hepatoma cell lines were grown in Dulbecco's modified Eagle medium (DMEM) plus 10% fetal calf serum. RNA was prepared using RNA-zol according to the manufacturer's recommended procedures (Tel-Test, Inc.). 20-30 μg of total RNA was used for RNase protection analysis as described previously (Liu et al., 1997).

For RT-PCR analysis of RNA from tumor cell lines, reverse transcription was performed using M-MLV reverse transcriptase (NEB) and oligonucleotide primer RP217 located in coding exon 7 (5'-CCT CTG AGC AGT CTT CAA GAG T-3'). The first strand cDNA sample was then amplified using two different sets of primers, one set (RP168 + RP217) was specific for RIZ1 and the other (RP216 + RP217) for RIZ2+RIZ1.

RP168 primer is located within exon 4 (5'-TGG CTG CGA TAT GTG AAT TG-3'). RP216 primer is located within exon 6 (5'-CAA CTG AAG ACA AGT GAG CCA GA-3').

In situ hybridization analysis of fixed breast tissues was carried out as described previously using digoxigenin-labeled probes (Ji et al., 1997). The RIZ1 antisense probe was a 0.5 kb fragment generated by T7 transcription of the amino terminal region of RIZ1 upstream of coding exon 1. The exon 7 antisense probe was a 0.5 kb fragment corresponding to amino acids 700-866 and was generated by Sp6 transcription. Sections were incubated with mouse anti-digoxigenin antibodies (Boehringer mannheim) followed by incubation with biotin-conjugated secondary rabbit antimouse antibodies (DAKO). The calorimetric detection was performed using the Universal LSAB Kit (DAKO) according to the manufacturer's instructions.

Conclusion:

A role for RIZ1 as a candidate tumor suppressor is suggested by two previous observations: RIZ1 maps to human chromosome band 1p36 and both RIZ1-related PR domain proteins are candidate tumor suppressors, because MDS1-EVI1 is disrupted in leukemia and BLIMP1 is a transcriptional repressor of *c-myc*. We provide here further evidence that RIZ1 is a candidate breast tumor suppressor. We show that RIZ1 deficiency occurs in human breast cancer.

Our data indicate that loss of RIZ1 expression may be common in human cancers, at least for breast cancer tissues and hepatoma cell lines where 80% of samples analyzed showed undetectable expression of RIZ1. It remains to be determined whether the loss of RIZ1 is correlated with LOH of 1p36. Southern blot analysis did not show evidence of gross abnormalities of RIZ1 genomic DNA in tumor cells (not shown). Inactivating RIZ1 gene expression rather than mutating RIZ1 protein structure, therefore, appears to be the basis of loss of RIZ1 in malignant cells. In the dozens of tumor cell lines examined to date, an intact RIZ2 protein was always found. Thus, relative to what appears to be negative selection against RIZ1 expression in tumor cells, the uniform presence of RIZ2 is striking, and may indicate a positive role for RIZ2 in oncogenesis. Two alternative forms of the RIZ1-related PR domain gene MDS1-EVI1 have previously been proposed to play opposite functional roles in

transformation (Soderholm et al., 1997). The need to maintain RIZ2 expression in tumor cells may explain the lack of gross mutations in *RIZ* gene because RIZ2 shares 89% of coding region with RIZ1. Of course, mutations in the PR region of RIZ1 should not affect RIZ2. Such mutations, however, must be subtle (undetectable by Southern-blot analysis). Moreover, if such mutations exist, they are likely to be rare, at least in hepatoma cell lines and breast cancers which primarily display a loss of RIZ1 transcript.

Future work will focus on establishing the relevance of the loss of RIZ1 to carcinogenesis by analyzing RIZ1 mutant mice which we have generated recently. Preliminary analysis of a small number of animals show that these RIZ1 mutant mice develop a broad and unusual spectrum of tumors later in life. Although breast cancer and hepatoma were not found, it may reflect the limited number of animals analyzed or a species difference that has previously been found in Rb knock-out mice that do not develop retinoblastoma (Clarke et al., 1992; Jacks et al., 1992; Lee et al., 1992). We will also study the mechanisms of loss of RIZ1 expression in human breast cancer. Finally, we will study whether reintroducing RIZ1 into breast tumor cells would inhibit tumor cell growth.

In conclusion, we have identified RIZ1 as a candidate tumor suppressor. RIZ1 may be useful for diagnosis and therapy of breast cancer and hepatoma, and perhaps of other human cancers as well.

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